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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,970	07/19/2002	Tai-Tung Yip	16866-38-1PC	6649

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,970	YIP ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,12,20 and 84-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 8, 12, 20 and 84-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to the Amendment

The Amendment filed on 09/19/2005 in response to the previous Non-Final Office Action (04/20/2005) is acknowledged and has been entered.

Claims 1, 8, 12, 20 and 84-88 are currently pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 1, 8, 12, 20 **remain** and **new** claims 84-88 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps in claims 1 and 13 are: a correlation step describing how the results of the method relate back to the preamble of the method objectives.

In response to the rejection, Applicants contend that as explained by the Examiner, the claims recite the correlation step of comparing cancer samples to BPH samples.

The amendment has been considered, but is not found persuasive.

While Applicants contend that the claims recite the correlation step of comparing cancer samples to BPH samples, the claims as amended do not appear to relate back to the preamble of the method objective. For example, the preamble of Claim 1 recites a method of aiding a prostate cancer diagnosis. Thus, it is unclear how one can correlate a comparison of markers present in prostate cancer versus benign prostate cancer and aiding in prostate cancer diagnosis. In the instant case, it appears that the correlation step in the claims, as amended, aid in the diagnosis of prostate cancer vs. benign prostate hyperplasia.

Claims 1, 8, 12, 20 **remain** and **new** claims 84-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of aiding a prostate cancer diagnosis comprising determining a test amount of a marker from blood, urine, serum, and tissue

extracts, wherein the marker is a polypeptide which is differentially expressed in a prostate cancer patient and a benign prostate hyperplasia patient and has an apparent molecular weight of 5304.10 Da, does not reasonably provide enablement for a method of aiding a cancer diagnosis comprising determining a test amount of a marker in any and/or all samples, wherein the marker is a polypeptide which is differentially expressed in a prostate cancer patient and a benign prostate hyperplasia patient and has an apparent molecular weight of less than 27,000 Da. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims read on method of aiding a cancer diagnosis comprising determining a test amount of a marker in any and/or all samples, wherein the marker is a polypeptide which is differentially expressed in a prostate cancer patient and a benign prostate hyperplasia patient and has an apparent molecular weight of less than 27,000 Da. Thus, the claims read on aiding a cancer diagnosis by determining in any sample any and/or all polypeptides which are differentially expressed in a prostate cancer patient and a benign prostate hyperplasia patient. Therefore, there must be a correlation between the sample and the polypeptides level in a patient suffering from prostate cancer vs. a patient suffering from benign prostate hyperplasia vs. a patient whom has no history of either of the two, i.e. control.

However, the scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to aiding a cancer diagnosis by determining in any sample any and/or all polypeptides which are differentially expressed in a prostate cancer patient and a benign prostate hyperplasia patient. The specification teaches (page 6, lines 26-34) that a marker in the context of the present invention refers to a polypeptide which is differentially present in a sample taken from a patient having prostate cancer as compared to a comparable sample taken from a subject who does not have prostate cancer (e.g. benign prostate hyperplasia patients or healthy subjects). For example, the specification discloses (beginning on page 30 to page 34, line 25) a number of polypeptides which where shown to be present in seminal plasma samples from patients with prostate cancer as compared to patients with BPH (benign prostate hyperplasia). Conversely, the specification appears to be silent on the presence of the polypeptides in samples taken from healthy patients. Thus, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to aiding prostate cancer diagnosis comprising detecting a polypeptide which is differentially expressed in a prostate cancer patient and a benign prostate hyperplasia patient, and applicant has not enabled the differential level of the polypeptide as a diagnostic for prostate cancer because it has not been shown that these levels are not present to some extent in healthy individuals.

For example, if the marker were a polypeptide generated by PSA-mediated proteolysis of semenogelin I, such as seminal basic, those of skill in the art would recognize the unpredictability of diagnosing a prostate cancer patient based on the differentiated level of the protein fragments in seminal fluid. For example, Lilja et al. (J. Bio. Chem. 1989; 264: 1894-1900) discloses semenogelin as a predominant protein in human semen. Specifically, the reference teaches that liquefaction of the seminal gel parallels proteomic fragmentation of semenogelin which is mainly due to the proteolytic activity of the prostate specific antigen (page 1894, 2nd column, 2nd paragraph). Moreover, Malm et al. (The Prostate 2000; 45: 132-139) examined the enzymatic action of prostate specific antigen and substrate specificity to semenogelin in semen (abstract). The reference teaches (page 133, 1st column, 1st paragraph) that in semen approximately two thirds of PSA remains enzymatically active, i.e., proteolysis of semenogelin, while the remaining 30% to 40% is inactive mainly due to internal cleavage and complexed PSA contributing only a small percent. In contrast,

Malm et al. disclose (page 133, 1st column, 1st paragraph) that in serum and blood PSA mainly occurs as a complex and clinically, these different forms are used to enhance the discrimination of men with benign prostate hyperplasia and prostate adenocarcinoma. Thus, one of skill in the art would recognize the need for a control because they would expect a polypeptide generated by PSA-mediated proteolysis of semenogelin I to be found in seminal fluid/semen of healthy individuals.

A review of the literature pertaining to prostate cancer diagnosis emphasizes the use of controls. Thus, if the determining step was based on proteomics, those of skill in the art would recognize the unpredictability of diagnosing a disease without a control. For example, Adam et al. (Cancer Research 2002; 62: 3609-3614) used proteomic profiling for detecting prostate cancer. Specifically, the reference teaches (page 3613, 1st column, 1st paragraph) that their successful development of a diagnostic system was achieved by using a large, carefully chosen training set of randomly selected samples and also, disclose the difficulties in selecting a cancer free control population because "healthy" men with normal PSA and normal DRE rarely undergo a prostate biopsy to be certain that the controls are truly negative. Adam et al. further teach (page 3613, 1st column, 2nd paragraph) that a "normalization" process is critical because most all of the protein alterations between cancer and non cancer cohorts are based on overexpression or under expression of proteins and not solely on their presence or absence. Furthermore, Paweletz et al. (Proc. Amer. Assoc. Cancer Research 1999; 40: 411) teach a novel, proteomic approach to monitor carcinogenic disease progression from cancer tissues. In the report, the authors found a highly reproducible protein fingerprint for three different cancers which defined protein expression changes from normal epithelium to pre-invasive carcinoma cells to actual invasive carcinoma in a cell-type and metastatic-specific manner. Thus, in view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

In response to the rejection, Applicants submit that the claims now recite a general MS procedure for distinguishing between the two disease states, e.g. prostate cancer and BPH. Thus, Applicants assert that the claims do not rely on identification of specific markers, but use the power of MS to generate profiles to quantify a plurality of proteins by size in a rapid const-effective manner. Moreover, Applicants argue that there is not longer any need to evaluate the data to determine what specific markers are present in the sample because they have limited the claims to

embrace the step of resolving a plurality of markers via MS and generating data based on molecular weight. Furthermore, Applicants argue that in view of the amendments, applicants have focused their claims and their invention to a scope that is clearly taught by examples and detailed teachings. For example, Applicants submit that the specification teaches that a MS generated mass profile generally capturing multiple proteins can, by virtue of the quality of the sized proteins, be a useful tool to distinguish between prostate cancers.

These arguments and amendments have been carefully considered, but are not found persuasive.

In the instant case, the Examiner agrees that MS is useful for generating profiles to quantify a plurality of proteins by size in a rapid cost effective manner and that the instant method is enabled for discriminating between prostate cancer and benign prostate cancer. However, as described above with respect to prostate cancer diagnosis, those of skill in the art recognize the importance of having a control sample, e.g. "healthy" or normal sample (see for example Adam et al. and Paweletz et al. both of which are of record). Thus, in the absence of a "healthy" or normal sample, how are the results obtained by practicing the active steps going to aid in the diagnosis of prostate cancer with any predictability. In other words, if a polypeptide generated by PSA-mediated proteolysis of semenogelin I, such as seminal basic is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some pattern that would allow the polypeptide to be used in a diagnostic manner. For example, many proteins such as seminal basic are expressed in human semen as well as in individuals with prostate cancer as evidenced by the disclosure and Lilja et al., above. Therefore, one needs to know that the plurality of proteins are present only in the cancer sample to the exclusion of the normal sample. Thus, in the absence of any correlation between the proteins with any known disease or disorder, any information obtained from various protein profiles in both normal and diseased tissue only serves as the basis for further research on the observation itself.

Amended Claims 1, 8, 12, 20 **remain** and **new** claims 84-88 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 10/221,905.

Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus. In the instant case, the specific protein markers having a molecular weight of 97402.68, 9752.30, 8766.93, 6277.97, or 2781.72 Da, claimed in the conflicting applications appears to fall within the same scope as the genus of a markers having an apparent molecular weight of less than 10,000 Da claimed in the application being examined and, therefore, a patent to the genus of a markers having an apparent molecular weight of less than 10,000 Da would necessarily, extend the rights of a specific marker should the application being examined issue as a patent after the conflicting application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants have not submitted an argument pointing out disagreements with the examiners contentions. As such, Claims 1, 8, 12, 20 and 84-88 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 10/221,905.

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
11/9/05